

Role of Cancer Protein Identified by Princeton, LBNL Teams at NSLS

Scientists working at the NSLS beamline X25 have unveiled the details of an important cancer protein. Though the protein, called Ski - for Sloan Kettering Institute, where it was identified in the early 1980s - is known to trigger tumor growth, how it does this is still not well understood. The new results, which are reported in the November 1, 2002 issue of *Cell*, shed light on this process and may provide ways to design new anticancer drugs.

"We now have a very important clue as to how Ski interferes with key proteins that prevent cells from becoming cancerous," says Yigong Shi, a molecular biologist at Princeton University. Shi leads one of the two teams, one from Princeton and one from Lawrence Berkeley National Laboratory (LBNL), that conducted the study,



Yigong Shi

which is supported by the National Institutes of Health and the Searle Scholar and the Rita Allen Foundations.

"Understanding how to stop Ski from disrupting the normal function of cells will probably be key to developing new anticancer drugs," continued Shi.

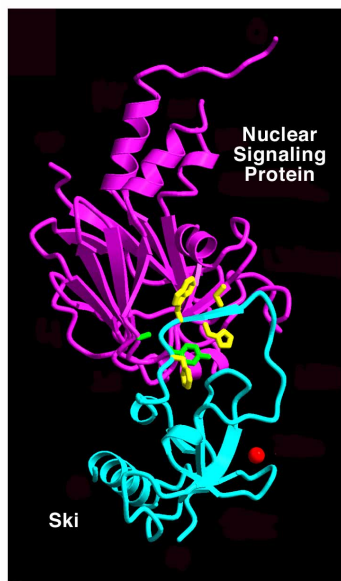
Ski prevents a protein called transforming growth factor-beta (TGF- β) from safeguarding cells against excessive growth.

"TGF- β acts like a molecular traffic light, ordering certain cells to slow down and stop dividing," Shi says. "When TGF- β is blocked, for example by Ski, cells manage to speed through this checkpoint, triggering runaway cellular growth that eventually results in cancerous tumors."

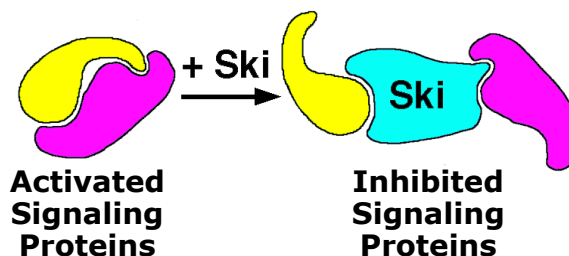
TGF- β cannot enter cells, so it transmits its signal inside the cell by attaching to receptor proteins on the cell's outer surface. The signal generated by this interaction is carried across the cell membrane to proteins inside the cell.

Some of these signaling proteins are triggered inside the cell cytoplasm and later bind to other proteins inside the nucleus. The combination of both types of signaling proteins activates genes necessary for the normal functioning of the cell.

Ski, which is already present in the human body, disrupts the signaling proteins when it is either overexpressed or introduced by a virus inside the body. The new



Overall structure of the complex of Ski and a nuclear signaling protein.



Schematic diagram of a proposed mechanism for the Ski-mediated repression of TGF- β signaling. By simultaneously binding to the cytoplasmic (yellow) and nuclear (purple) signaling proteins, Ski prevents the two signaling proteins from binding to each other, thus suppressing the action of TGF- β .

study focused on the first of these two possible processes.

"Scientists have previously shown that Ski disrupts normal cell functioning by directly disrupting the expression of genes inside the cell's nucleus," Shi says. "But nobody has ever investigated whether Ski could disrupt the signaling proteins that activate the genes."

The Princeton team looked at the molecular details of a complex

made of Ski and nuclear signaling proteins by using x-rays generated at the NSLS.

The researchers saw that, as they had suspected, Ski disrupts the cytoplasmic signaling proteins, so that when Ski binds to the nuclear signaling proteins, the cytoplasmic signaling proteins cannot attach to their nuclear counterparts. "This binding process is probably one of the major ways in which Ski disrupts the signaling proteins and,

thus, suppress the action of TGF- β ," Shi says.

The LBNL team performed various biochemical tests that confirmed these results by also showing that Ski binds to nuclear signaling proteins.

-Patrice Pages

[Editor's note: Reprinted with permission from the BNL Bulletin - November 1, 2002.]